Coverage Position:

CIGNA HealthCare does not cover prostate saturation biopsy because it is considered experimental, investigational or unproven.

General Background

Prostate cancer is the most common cancer diagnosed in North American men, excluding skin cancers. It is estimated that in 2007, approximately 218,890 new cases and 27,050 prostate cancer-related deaths will occur in the United States (National Cancer Institute [NCI], 2007a). Prostate cancer is the second leading cause of cancer death in men, exceeded only by lung cancer. It accounts for 29% of all male cancers and 9% of male cancer-related deaths. Prostate cancer is rare in men younger than age 50, and incidence rises rapidly with each subsequent decade. The age-adjusted incidence rate is higher in

African-American men compared to white males. Mortality from the disease is higher in African-American males, even after adjusting for access-to-care factors. Risk factors for prostate cancer include family history, as well as age and race. Other possible risk factors include alcohol consumption, vitamin or mineral interactions, and other dietary habits (NCI, 2007a).

Screening of asymptomatic men for prostate cancer has become a widespread practice in the United States.

Screening procedures used for prostate cancer screening include digital rectal examination (DRE) and prostate-specific antigen (PSA). In situations of an abnormal DRE and/ or elevated PSA, a transrectal ultrasound (TRUS)-guided prostate biopsy is usually performed. Prostate biopsy is used to diagnose prostate cancer, as well as in staging of the condition. In general, prostate biopsies are considered safe and are usually performed in an outpatient setting. The more common complications from prostate biopsies include: hematuria, hematospermia, and hematochezia. Other complications are rare and are more severe, including: severe bleeding, prostatitis, sepsis, urinary retention, and vasovagal reactions.

The prostate biopsy samples the areas of the prostate gland where tumors are most frequent, in a systematic manner. The biopsy is not lesion directed. The ultrasound is used to guide the biopsy needle into different areas of the gland rather than identifying lesions. The traditional prostate biopsy was the sextant biopsy, which involves taking six biopsies in a parasagittal line drawn halfway between the lateral border and midline bilaterally, from the base, mid-gland, and apex, with a 20-25% positive biopsy rate (Raja, et al., 2005).

It was thought that the sextant technique was inaccurate mainly because it undersampled the peripheral zone of the prostate. Modifications of the sextant biopsy have been developed and reported on in the literature. The modified sextant biopsy protocol involves moving the middle biopsies of the standard sextant laterally and the biopsy trajectories angled anterolaterally so that mainly the peripheral zone is sampled. This method appeared to improve the cancer detection rate (Raja, et al.,2005). Extended biopsy techniques that utilized additional cores directed to the peripheral zone have been developed. It has been noted that the sensitivity of prostate cancer screening may be improved by taking 10-12 cores rather than six cores. Taking 10 to 12 tissue cores has become the standard of care (Wilson and Crawford, 2004). Sextant and extended biopsy with 10-12 cores is generally performed with local anesthesia. It has been estimated that up to 31% of all non-palpable prostate cancers diagnosed with needle biopsy and treated with radical prostatectomy are potentially insignificant tumors, with volumes less than 0.5 cm3 (Djavan et al., 2003). In some situations, there may be a continuing suspicion of prostate cancer even with repeated negative prostate biopsies. The prostate saturation biopsy has been proposed for circumstances where the patient is considered high-risk for prostate cancer, but biopsies have been negative. The saturation biopsy involves taking between 20 to 40 core biopsies. Additional cores may be taken for larger prostates. It is theorized that the saturation biopsy may detect cancer that was not detected with a prior biopsy. The technique is similar to the sextant or the extended biopsy in that it is performed during a TRUS, utilizing the core needle biopsy device. Some type of regional or general anesthesia or intravenous sedation is typically used. Another method of performing saturation biopsy involves utilizing a transperineal, grid-based method

using a brachytherapy template. This method is theorized to be more systematic and allows for improved sampling of the area immediately anterior to the urethra (Raja, et al., 2006). The saturation biopsy is based on the assumption that the cancer is small and/or located in one of the deeper reaches of the gland (Raja, et al., 2006). The whole gland is sampled without following any particular zonal pattern. It is thought that the larger number of evenly distributed samples increases the probability of detecting an underlying cancer, regardless of the tumor size or location. Increased bleeding is generally noted with an increased amount of core biopsies (Routh and Leibovich, 2005). A concern with this type of biopsy approach is the possibility of an increased risk of detecting clinically insignificant cancers which may lead to unnecessary treatment.

It has been noted in the literature that controversy exists regarding which zones of the prostate to sample during a biopsy and how many cores to obtain that will minimize the diagnosis of clinically insignificant cancers. Various interrelated factors are involved in the decisions of when to biopsy and when to perform a repeat biopsy. These factors include: the PSA level, age of patient, family history, size of prostate, and the location and type of prior biopsies. It has been noted in the literature that, although prostate needle biopsy is considered the gold standard for cancer diagnosis, it is impossible to verify the absence of cancer in the prostate in vivo; as a result, the true false-negative rate remains unknown (Chrouser and

Lieber, 2004). It appears that increasing the number of biopsies may be associated with increased risk due to an increase in complications (Raja, et al., 2005). Review of the literature does not indicate that the prostate saturation biopsy is more effective than an extended prostate biopsy for the detection of clinically

significant prostate cancer or that use of this test will lead to an increase in survival or prognostic yield.

Literature Review

Stewart et al. (2001) conducted a study based on the hypothesis that markedly increasing the number of cores obtained during prostate needle biopsy may improve the cancer detection rate in men with persistent indications for repeat biopsy. Saturation TRUS-guided biopsy was performed in 224 men. The mean number of previous sextant biopsy sessions was 1.8 (range one to seven). The median years from the first biopsy until the saturation biopsy was performed were 2.4 years.A mean of 23 saturation biopsy cores (range 14-45) were distributed throughout the whole prostate including the peripheral, medial and anterior regions. Indications for repeat biopsy included persistently elevated PSA levels in 108 cases and persistently elevated PSA and abnormal rectal exam in 27 patients, and persistently abnormal rectal examination in four patients, high grade prostatic intraepithelial neoplasia (PIN) in the previous biopsy in 64 patients, and atypia in the previous biopsy in 21 patients. In 112 of the 224 men (50%), it was noted that they had only a single set of negative biopsies before undergoing the saturation biopsy. It was noted that cancer was detected in 77 of the 224 patients (34%). Of the 77 patients in whom cancer was detected, 52 underwent radical prostatectomy. The location where the cancer was detected with the saturation biopsy was not reported. The complication rate for saturation biopsy was 12% and hematuria requiring hospital admission was the most common event. The authors concluded that saturation needle biopsy of the prostate is a useful diagnostic technique in men at risk for prostate cancer with previous negative office biopsies. Grossklaus et al. (2001) conducted a retrospective case review of the results from 135 consecutive patients who underwent

radical retropubic prostatectomy (RRP). Needle biopsy data, including the number of cores, percentage of positive cores, laterality of the positive cores and Gleason sum were compared with the pathological data of the RRP specimen. The data was further separated into those with six or fewer cores (96 men) from those with more than six cores (39 men). It was noted that there was no significant relationship between the number of cores obtained and the predicted pathology of the RRP specimen. There did not appear to be a difference in the number of positive cores, bilateral positive cores or percentage tumor in the cores between men with more or less than six biopsies. It was noted that the percentage of positive cores may be the best predictor of pathological stage and tumor volume.

The authors concluded that taking more prostate needle biopsy cores seems to improve the detection of prostate cancer, but there appears to be no major improvement in prognostic information over that gained with traditional sextant biopsies. Fleshner and Klotz (2002) conducted a study to determine the role of saturation prostate biopsy among selected men with unexplained worrisome PSA parameters. The study involved 37 men who underwent saturation biopsy. This involved obtaining 24 peripheral zone cores, six to 12 transition zone cores and two lateral lobe transurethral samples. All of the men had previously undergone at least three prior sets of TRUS prostate biopsies. The median PSA level and the percent-free PSA level was 22.4 ng/ml (range 7.8-73.8) and 0.11 (range 0.04-0.17), respectively. The specimens were sent for pathologic examination in sets of six in order to determine the marginal benefit of additional sampling. After pathologic examination, it was noted that five patients (13.5%) had detectable carcinoma. In all cases, the carcinoma was detected in the 18 peripheral zone cores. Acute prostatitis was noted in 19% of the specimens. The study concluded that most men with multiple previous biopsies and

increasingly worrisome PSA parameters do not have cancer and that the marginal utility of the saturation biopsy is low. It was noted that although rare additional cases may be detected using this technique, 18-core peripheral sampling is recommended for those difficult diagnostic cases. Sur et al. (2004) conducted a prospective randomized study to compare standard prostate biopsy to extensive biopsy utilizing intravenous conscious sedation (IVCS). Initial biopsy patients (n=l97) were randomized to either standard biopsy (i.e., 6-12 biopsies, mean 10.1) using intrarectal lidocaine gel, or extensive biopsy (i.e., 20 biopsies) using IVCS. The objective was to determine if the extensive biopsy technique resulted in a higher rate of cancer detection and/or improved patient tolerance of the biopsy procedure compared to a more standard biopsy technique. Eighty-eight patients (48%), underwent the standard biopsy, and 94 (52%) underwent the 24-core extensive biopsy, with 15 patients withdrawing from the study. The authors note that while the sextant biopsy with six core samples may not be sufficient, the optimal number of biopsies required to maximize cancer detection without over-detection of clinically insignificant cancers is still uncertain. It was noted that the extensive prostate biopsy with 24 cores did not improve cancer detection rates compared to a standard biopsy technique in which an average of 10 cores was obtained. The IVCS technique was well tolerated and associated with significantly less pain and greater patient satisfaction than the rectal lidocaine gel alone. The authors note that the results imply that saturation biopsy is not necessary in patients undergoing initial prostate biopsy so long as extended biopsy that includes 8-12 cores is utilized.

Rabbets et al. (2004) reported on the diagnostic yield of office saturation biopsy in patients at increased risk for prostate cancer and at least one negative prior biopsy. Saturation

prostate biopsy was performed on 116 patients with at least one prior negative biopsy and with certain risk factors, including persistently elevated prostate specific antigen, abnormal DRE, or prior atypia or PIN on a prior biopsy. A total of 34 cancers were detected for an overall diagnostic yield of 29%. In this series, only 22% of the patients had undergone prior sextant biopsies. In a small cohort, it was noted that there was a 64% cancer detection rate (seven of 11) in patients who had undergone a previous sextant biopsy. The authors concluded that saturation biopsy has a significant cancer detection rate even in patients who have undergone prior biopsies with more extensive lateral sampling.

Epstein et al. (2005) conducted a review of 103 men who had been predicted to have insignificant cancer in their radical prostatectomy (RP) specimen. The aim of the study was to determine whether saturation biopsy of the prostate could reliably predict insignificant and significant cancer in men who were candidates for watchful waiting. Candidates were identified based on the preoperative needle biopsy pathologic findings and serum PSA levels. The patients had limited cancer on the routine needle biopsy: no core with more than 50% involvement; Gleason score less than seven; and fewer than three cores involved. Saturation biopsy with an average of 44 cores and an alternate biopsy saturation scheme with one half of the number of cores were performed in the pathology laboratory on the RP sections. Of the tumors, 97% were organ-confined. The RP Gleason score was less than seven in 84% of the cases. Of the cancer specimens, it was noted that 71% were insignificant, and 29% had been incorrectly classified before surgery using standard biopsy schemes. Using the full saturation biopsy scheme, and where significant cancer was predicted, the probability of having insignificant cancer appeared to be 11.5% (i.e., false-positive

rate). If the algorithm model predicted insignificant cancer, the significant cancer was also only 11.5% (i.e., using the alternate biopsy sampling scheme, the false-positive rate was 8%, and the false-negative rate was 11.4%).

The authors note that the results of the current study need to be prospectively evaluated to determine their validity. In addition, further testing would be required of the algorithm with saturation biopsy of patients in vivo. It was also noted that the classification of insignificant and significant cancer did not necessarily predict the biologic behavior of cancer long-term.

Jones et al. (2006) reported on results of a sequential cohort study that compared office-based saturation prostate biopsy to traditional 10-core sampling as an initial biopsy. *A* 24-core biopsy was performed on 139 patients undergoing initial prostate biopsy. Indication for the biopsy was an increased PSA of 2.5 ng/ di or greater in all patients. The results were compared to 87 patients who had undergone 10-core initial biopsies. Cancer was detected in 62 of the 139 patients (44.6%) who underwent the saturation biopsy and 45 of the 87 patients (51.7%) who underwent 10-core biopsy. The study notes that breakdown by PSA level failed to show benefit to the saturation technique for any degree of PSA increase. The authors concluded that the saturation technique did not appear to offer benefit as an initial biopsy technique and that further efforts at extended biopsy strategies beyond 10-12 cores are not appropriate as an initial biopsy strategy. Meng et al. (2006) investigated the impact of the greater number of prostate biopsies on the nature of cancer identified. **The authors noted that increasing the number of cores obtained at the time of TRUS-guided biopsy has increased the number of cancers identified; however, there is also increasing recognition that many men with prostate cancer may not benefit from early aggressive intervention**

and that over-detection of prostate cancer has resulted in over-treatment.

The Cancer of the Prostate Strategic Urologic Research Endeavor database, a longitudinal disease registry of men with prostate cancer, was utilized to identify 4072 men with six or more prostate biopsies obtained at initial diagnosis. Of these patients, 30%, 47% and 24% underwent 6, 7 to 11, and more than 12 biopsies, respectively.

There was a significant correlation noted between the biopsies and numerous sociodemographic and clinical variables, including PSA, comorbidities and income. It did not appear that there was a difference in disease characteristics as assessed by Kattan and Caner of the Prostate Risk Assessment scores among men with a biopsy number between six and 17. In a subset of 1548 men who underwent radical prostatectomy, no differences were observed regarding biochemical-free survival ata follow-up of 2.2 years.

The authors concluded that, "The increasing number of prostate biopsies obtained at diagnosis increases cancer detection but the impact on disease characteristics remains unclear. Our data suggest that the risk stratification of prostate cancers is independent of biopsy number (6 or greater) in a contemporary cohort of men." Bott et al. (2006) reported on a case series to describe a modified saturation biopsy technique and results of extensive transperineal template prostate biopsies in men with a high risk of prostate cancer for whom repeated transrectal biopsies were not diagnostic. The study included 60 men who had a rising PSA level and had at least two sets of benign octant biopsies or two or more prior biopsies containing high-grade prostatic intraepithelial neoplasia or atypical small

acinar proliferation. In a transverse image, the prostate was divided into six regions. Three to five transperineal biopsy cores were taken in each of the six regions with the use of a brachytherapy template. Cancer was detected in 23 (38%) men. Of this group, cancer was detected in the anterior region of the prostate alone in 12 men (60%). One patient required overnight admission for hematuria, and two developed urinary retention. There were no reported cases of sepsis. The authors concluded that, "In men with a clinical suspicion of prostate cancer, but benign or equivocal prostate biopsies, extensive transperineal template biopsy of the prostate is a useful diagnostic tool. It allows sampling of the whole prostate in a systematic and safe fashion." Walz et al. (2006) conducted a study of 161 men who underwent saturation biopsies to explore the yield of saturation biopsy and developed a nomogram to predict the probability of prostate cancer on the basis of saturation biopsy. The biopsy involved obtaining an average of 24 cores and was performed in men with persistently elevated PSA levels. All had at least two previously negative, eight-core biopsies.

Prostate cancer was detected in 41% (n=66). Positive cores were found mainly in the far lateral zone (79%), the media-lateral zone (36%) and the transition zone (18%). It was reported that the rate of insignificant cancers was 15.6%, or five of the 32 men treated with radical prostatectomy; however, the assessment of clinical significance could only be assessed for those who underwent prostatectomy and could not be assessed for the remaining 34 patients. The complication rate was noted to be 2.5% and included two acute urinary retentions, one acute prostatitis and one reactive syncopal episode. Two hospitalizations for intravenous antibiotics were required. The results indicated that PSA density and transition zone volume were the most significant predictors of prostate

cancer. The authors concluded that saturation biopsy may be indicated in men with a persistent suspicion of prostate cancer. Merrick et al. (20006) reported on a study of 102 patients to determine the prostate cancer incidence, anatomic distribution, Gleason score profile, and tumor burden in patients diagnosed by transperineal template-guided saturation biopsy. All but one of the patients had undergone at least one prior negative TRUS biopsy. On average, patients had undergone 2.1 prior negative TRUS biopsies with a mean of 22.4 core biopsies. The prostate gland was divided into 24 regions for the biopsy, and the median number of cores taken was 50. Prostate cancer was diagnosed in 43 patients (42.2%). It appeared that there was considerable anatomic variability in prostate cancer distribution, with no anatomic region of the prostate without cancer. Complications included urinary retention in 38% of the patients who required a urinary catheter overnight, six for two days, and three for six days. Hematuria was noted in one patient who required overnight hospitalization. In their analysis, the authors noted that transperineal template-guided saturation biopsy "results in promising diagnostic yields for patients with prior negative TRUS biopsies. However, ideal patient selection, optimal transperineal saturation biopsy technique, number of biopsy cores, and regions to be sampled remains to be clarified."

Eichler et al. (2006) conducted a systematic review to compare the cancer detection rates and complications of different extended prostate biopsy schemes. Eighty-seven studies were analyzed with a total of 20,698 patients. Data was pooled from 68 studies that compared a total of 94 extended schemes with the standard sextant scheme. It was noted that increasing the number of cores was significantly associated with the cancer yield. Laterally directed cores appeared to increase the yield significantly, whereas centrally directed cores did not appear

to. Biopsy schemes with 12 cores that took additional laterally directed cores detected 31% more cancers than the sextant scheme. Biopsy schemes with 18 to 24 cores did not detect significantly more cancers. Adverse events for schemes up to 12 cores were similar to those for the sextant pattern. Adverse event reporting was poor for schemes with 18 to 24 cores. The authors concluded that prostate biopsy schemes consisting of 12 cores that add laterally directed cores to the standard sextant scheme strike the balance between the cancer detection rate and adverse events and that taking more than 12 cores does not add significant benefit.

Professional Societies/Organizations

National Comprehensive Cancer Network (NCCN): The NCCN published clinical practice guidelines for early detection of prostate cancer. The guidelines include an algorithm for follow-up of TRUS-guided biopsies. This algorithm includes recommendations for when extended-pattern biopsy, defined as 12 cores, is to be performed for initial and repeat biopsies. The recommendations include the following (NCCN, 2006):

- The number of cores in extended pattern biopsy includes:
  - ☐ Sextant (6 cores)
  - ☐ Lateral peripheral zone (6 cores)
  - ☐ Lesion-directed at palpable nodule or suspicious image
- Transition zone biopsy is not supported in routine biopsy. However, the addition of a transition zone biopsy to an extended biopsy protocol may be considered in a repeat biopsy if PSA is persistently elevated.
- After two negative extended TRUS biopsies, prostate cancer is not commonly found at repeat biopsy.
- For high-risk men with multiple negative biopsies, consideration can be given to a saturation biopsy strategy.

U.S. Preventive Services Task Force (USPSTF): The USPSTF published clinical guidelines: Screening for prostate cancer: Recommendations and rationale. The guidelines do not discuss prostate biopsies, but includes the following statements regarding biopsies: "DRE and PSA are the two principal tests currently used in the United States to screen for prostate cancer. Determining test characteristics of anyscreening test for prostate cancer is difficult because clinicians disagree on which cancers are "clinically important," and thus disagree on an appropriate target for early detection. The gold standard often used in screening studies-needle biopsy-may miss cancers that are present. Conversely, needle biopsy may serendipitously detect cancers unrelated to abnormal screening results. Especially in asymptomatic older men, screening with DRE and PSA may detect cancers that appear clinically significant based on size and tumor grade, but which would not have progressed to clinical symptoms during the patient's lifetime."

Summary

The prostate saturation biopsy has been proposed as a diagnostic tool for a subgroup of high-risk patients in whom prior conventional prostate biopsies have been negative. The aim of this technique is to improve cancer detection rates in these individuals. It has been proposed that the larger number of evenly distributed samples may increase the probability of detecting an underlying cancer, regardless of the tumor size or location. The role of prostate saturation biopsy in the detection of prostate cancer has not yet been established. It is not known whether this method improves the health outcomes of individuals.

There is a concern with this type of biopsy that there is an increased risk of detecting clinically insignificant cancers which

may lead to unnecessary treatment. It appears that there may be an increased risk associated with an increase in the number of cores obtained. There is no consensus regarding which zones of the prostate to sample during a biopsy and how many cores to obtain that will minimize the diagnosis of clinically insignificant cancers. It has not been demonstrated in the published peer-reviewed literature that the prostate saturation biopsy is more effective than an extended prostate biopsy for the detection of clinically significant prostate cancer, or that use of this test will lead to an increase in survival or prognostic yield.

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